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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,664	RASHTCHIAN ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-31,33,35-39 and 44-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-31, 33, 35-39, and 44-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-3, 5-31, 33, 35-39, and 44-59 are pending in the instant application. Claims 34 and 40-43 have been canceled in applicant's amendment filed 4/5/2004. The amendment and arguments have been thoroughly reviewed but are not sufficient to place the instant application in condition for allowance. The following rejections are reiterated and constitute the complete set being presently applied to the instant application. Any rejection under 35 USC 102 or 103 not reiterated is withdrawn in view of the cancellation of the claims. Response to applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections and Objections

3. The objection to claims 40-43 made in section 3 of the previous office action is withdrawn in view of the cancellation of the claims.

4. The objection to the specification and the new matter rejection made in section 6 of the previous office action are withdrawn in view of applicant's arguments.

MAINTAINED REJECTIONS

Written Description

5. Claims 5-23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to compositions generally comprising any mutant DNA polymerase of Taq, Tne, Tma, Pfu, Pwo, VENT, and DEEPVENT. These compositions comprise an extremely large number of mutant DNA polymerases, which the specification does not describe, and also includes mutant polymerases that have not been taught in either the specification *or* the art. The mere recitation that mutant DNA polymerases are part of the invention is not a description of the mutant polymerases themselves and is not representative of the large number genus of polymerases encompassed by the claims. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed mutant polymerases, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to

mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

6. The response traverses the rejection. Firstly, it is noted that with regard to applicant's citation of the various case law on pages 16 and 17 of the response, such decisions were made before the *Regents of Univ. of Ca. V. Eli Lilly* (Fed. Cir. 1997) decision on which the written description guidelines are based. The response traverses that the specification describes a number of representative examples of the claimed genus of polymerases and cites the specifications teachings. The response asserts that "in so doing, the 'representative number' standard under Eli Lilly is clearly met." This argument has been thoroughly reviewed but was found unpersuasive. The claims are drawn to compositions that are generally drawn to any "mutant polymerase" and which also comprise additional, noninventive reagents that would be used in, for example, well known sequencing or PCR reactions. As such, the claims are effectively drawn to a composition containing any 'mutant' polymerase. Such recitation not only

encompasses the examples taught in the specification, but any mutant polymerases that had not been discovered, contemplated, or constructed at the time of applicant's invention. For example, US Patent 6,346,379 to Gelfand et al; issued 2/12/2002, teaches of an aspartate to lysine mutation at position 4 of the critical motif described by Gelfand et al which results in a thermostable DNA polymerase which has a level of discrimination against incorporation of nucleotides labeled with fluorescein family dyes which is reduced in comparison to the native form of the polymerase. Such a mutant is not even contemplated by the instant specification. It is clear that further, unpredictable, novel, and unobvious mutations in polymerases have been made since the time the instant invention was filed, which have not been described or contemplated by the specification. Additionally, the mutant polymerases taught in the prior art and in the specification are not 'representative' of the mutant polymerase taught by Gelfand as the mutation is not "represented" by any of the mutations summarized in the specification, nor is the alteration in activity of the polymerase contemplated or taught by the specification. In response to the citation of *Hybridtech Inc.*, the polymerase of Gelfand represents a polymerase that was not conventional or well known to one of ordinary skill, therefore, the citation of *Hybridtech Inc.* is misapplied in the instant response. Additionally, the inventive mutations taught by Gelfand, are not considered a mere "nuance" (with regard to the citation of *In re Alton*) nor does it represent a mutation that 'might be fairly deduced from the original application' (with regard to the citation of *Ex Parte Parks* and *In re Alton*, as well as *Acme Highway Products Corp*, and *Westphal*). For these reasons and the reasons made of record above and in the previous office action, the rejection is maintained.

Claim Rejections - 35 USC § 102

7. Claims 1, 44, 48, and 53-54 are rejected under 35 USC 102(b) as being anticipated by Scalice.

Scalice teaches a composition containing Taq DNA polymerase (50 U/mL), Tris buffer with MgCl, Nonidet P-40 nonionic surfactant, Tween (53-54), and an antibody (claim 44) which binds to Taq polymerase (see col. 15, lines 42-55). Scalice also inherently teaches the limitation recited in claim 48 that the composition is stable upon storage as the composition of Scalice is the same as that of the instant claims and therefore the compositions have the same characteristics. Further, the composition taught by Scalice must be stable upon storage for some length of time because it is stable under the cycling temperatures of the PCR reaction such that the polymerase retains activity and the reagents are stable to allow amplification of a target nucleic acid.

Response to arguments

8. The response traverses the rejection. The response traverses that the term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. This argument has been thoroughly reviewed but was not found persuasive. Firstly, the recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as…)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Additionally, the preamble of the claim merely recites an intended use of the claimed composition, which does not limit the components or the amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable

interpretation, the term is interpreted to encompass for example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master solution such that any dilution of the master solution would result in the reagents being present and ready for use in a reaction without need for further addition of those reagents. In other words, the reagents are present at concentrations to function in a master solution. The master solution could be one for use in "nucleic acid synthesis, nucleic acid amplification, sequencing, or restriction digestion". Accordingly, as the composition of Scalice teaches all of the components of the claimed compositions, Scalice anticipates the claimed invention. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

9. Claims 1-3, 5, 8, 24-28, 30, 31, 35, and 48-59 are rejected under 35 USC 102(b) as being anticipated by Vizard.

Vizard teaches a composition for use in nucleic acid sequencing which contains a thermostable polymerase (Taq) at from 100-500 U/mL, a salt buffer which includes a magnesium salt, dNTPs (up to 150 μM; the recitation of "about 200-about 300 μM" is broadly interpreted to encompass 150μM), ddNTPs, and non ionic detergents such Triton X-100 (see p 3-5). Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. Vizard inherently teaches the limitation recited in claims 24 and 25

that the polymerase retains 90% activity for at least 4 weeks when stored at 20 or 25 C and for at least a year when stored at 4C because the composition of the claims and the composition of Vizard are the same and therefore the compositions have the same characteristics. Vizard also inherently teaches the limitation recited in claims 48 and 49 that the composition is stable upon storage as the composition of Vizard are the same as that of the instant claims and therefore the compositions have the same characteristics. Further, Vizard teaches that the composition is stable on storage (p. 7).

Response to arguments

10. The response traverses the rejection. The response asserts that because Vizard teaches that the composition is a "concentrate", that Vizard cannot anticipate the claimed invention under *Kalman v Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983) because Vizard does not teach reagents at "working concentrations" as defined by the specification and common use in the art. This argument has been thoroughly reviewed but was found unpersuasive. The term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. The recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as amplification, sequencing, or digestion of nucleic acids)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Further, the term working concentration is not commonly used in the art to limit "functions" only to amplification, sequencing, or digestion of nucleic acids. The preambles of the claims merely recite an intended use of the claimed composition, which does not limit the

components or the amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable interpretation, the term is interpreted to encompass for example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master solution such that any dilution of the master solution would result in the reagents being present and ready for use in a reaction , in relation to each other, without need for further addition of those reagents. In other words, the reagents are present at concentrations to function in a master solution, and are therefore 'at a concentration to perform a particular function'. The master solution could be one for use in "nucleic acid synthesis, nucleic acid amplification, sequencing, or restriction digestion" as set forth in the preamble. As the recitation of 'working concentration' is not limited in the art to be used only to define the concentration of a reagent while it is performing in a sequencing or amplification reaction, and the examiner has used the definition in the specification in interpreting the recitation, it is clear that the term does not limit the compositions to exclude the concentrations taught by Vizard. It is further noted that the concentrations of reagents used in the compositions of Vizard could be used in nucleic acid sequencing and amplification reactions at the concentrations listed in the 'concentrate'.

In response to applicant's argument that it "is entirely proper to use the specification in order to determine what the inventor means by terms and phrases" citing *Laitram Corp*, as evidenced by the analysis above, the examiner has given the term it's broadest reasonable interpretation given the definition in the specification. However, applicants are reminded that while the claims are read in light of the specification, limitations from the specification are not read into the claims. Although the claims are interpreted in light of the specification, limitations

from the specification are not read into the claims. *In re Van Geuns*, 988 F.2d 1181,26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the examiner has used the *definition* of 'working concentration' in the specification to interpret the term in the claims, however, express limitations (ie, examples of 'functions') have not been read into the claims. It is additionally noted that the *concentrate* (as emphasized in the response) of Vizard teaches concentrations of polymerase which overlap the scope of the concentrations set forth in the rejected dependent claims (claim 8 recites .1 to 200 units per milliliter and Vizard teaches a composition where polymerase is 100 to 500 units per milliliter). As noted in *In re Spada*, 911 F.2d 705,709,15 USPQ2d 1655, 1658 (Fed. Cir. 1990) "Products of identical chemical composition can have mutually exclusive properties". A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant claims are necessarily present (see MPEP 2112.01 II, May 2004 edition). It appears that applicant is arguing that because the use for the solution is different from the one intended by applicant, that Vizard does not anticipate the claimed invention. However, the intended use for a composition or a kit does not carry patentable weight. Additionally, for the instantly claimed compositions to perform any of the intended uses argued by applicant, dilution however small, will be required in the form of adding nucleic acids to the compositions. Therefore the argument that Vizard teaches a concentrate is not found persuasive because the argument is based on the fact that the composition of Vizard requires dilution, which will occur to the instantly claimed compositions when they perform the intended use exemplified in the instant specification. Furthermore, the claims are drawn to products and kits and methods not requiring any particular series of steps. The concentrations of reagents used in the compositions of Vizard could be used in nucleic acid

sequencing and amplification reactions at the concentrations listed in the 'concentrate'. For these reasons, applicant's arguments that Vizard does not teach compositions at working concentrations that contain no nucleic acid and the argument against the inherent properties of the composition of Vizard are not found persuasive. For these reasons and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

Claim Rejections - 35 USC § 103

11. Claim 29 is rejected under 35 USC 103(a) as being unpatentable over Vizard in view of Soderlund.

Vizard teaches a composition for use in nucleic acid sequencing which contains a thermostable polymerase (Taq) at from 100-500 U/mL, a salt buffer which includes a magnesium salt, dNTPs (up to 150 μM; the recitation of "about 200-about 300 μM" is broadly interpreted to encompass 150μM), ddNTPs, and non ionic detergents such Triton X-100 (see p 3-5). Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user.

Vizard does not teach concentrations of ddNTPs at concentrations of about .08-about 5 μM. However, Soderlund demonstrates sequencing of DNA in primer extension reactions where the concentration of ddNTPs is about 1 μM. Therefore, it would have bee prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of

Vizard in view of Soderlund to include compositions wherein the ddNTPs were present at 1 μM as taught by Soderlund for the expected advantage of using an effective amount of ddNTPs to achieve sequencing, in for example, a primer extension reaction, without wasting unnecessary extra ddNTPs. The ordinary artisan would have been motivated to determine the concentration of ddNTPs needed to carry out effective sequencing for the purposes of not wasting reagents. As stated in the MPEP (2144.05),

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")".

Further, as Soderlund teaches sequencing in primer extension reactions, for example, can be achieved with 1 μM ddNTPs, the ordinary artisan would have had a reasonable expectation of success that sequencing reactions could function at such concentration.

Response to arguments

12. The response traverses the rejection. The response asserts that because Vizard does not disclose, suggest, or otherwise contemplate compositions comprising a mixture of reagents at working concentrations wherein the concentration of the ddNTP is about 0.08 to about 5 micromolar, it is seriously deficient as a primary reference. The response then asserts that Soderlund does not teach the preparation of compositions comprising a mixture of reagents at working concentrations having no nucleic acid molecules where the concentration of ddNTP is

0.08 to about 5 micromolar, Vizard alone or in combination with Soderlund would not lead one of ordinary skill in the art to applicant's invention. This argument has been thoroughly reviewed but not found persuasive. Firstly, as noted in the MPEP 2143.01 (May 2004 edition), in *Ruiz v. A.B. Chance Co.,* 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004), the court rejected the notion that "an express written motivation to combine must appear in the prior art references…". It is additionally noted, as stated in the MPEP 2145, "One cannot show non obviousness by attacking references individually where the rejections are based on a combination of references. *In re Keller,* 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 (USPQ 375 (Fed. Cir. 1986).

The response further asserts that the examiner's attempted explanation appears to misconstrue the standard for obviousness where the required motivation must come from either the references themselves or in the knowledge generally available in the art. The response further asserts that the examiner's motivation of determining optimal concentrations for the purpose of not wasting reagents misses the point of obviousness. These arguments have been thoroughly reviewed by were found unpersuasive. Firstly, with regard to "required motivation coming from the references themselves", as stated above, express written motivation to combine is not required to appear in the prior art references. Secondly, with regard to the general knowledge available in the art, it appears that applicants are arguing that it was not generally known in the art that using the amount of reagent necessary to perform a given task would reduce waste, that practitioners would not be motivated to minimize waste of reagents, and that it was not generally known in the art that minimizing waste is of concern. This argument has been thoroughly reviewed but was found unpersuasive. The motivation to minimize waste and the

inherent benefit of reducing cost that such minimization would provide, was a concern generally known and shared by many of ordinary in the art at the time the invention was made. Further, it is noted that the number of teachings in the art of generating compositions for nucleic acid sequencing or PCR reactions was very high at the time of applicant's invention, and that, as noted in the previous office action, the concentrations of ddNTP as listed in the claims represents routine optimization which the courts have established in *In re Aller* does not support patentability unless there is evidence indicating such concentration is critical. In the instant case, no such evidence has been presented. For these reasons, and the reasons made of record above and in the previous office action, the rejection is maintained.

13. Claim 36 is rejected under 35 USC 103(a) as being unpatentable over Sorge in view of Slatko.

Sorge teaches a method for nucleic acid amplification by PCR comprising contacting a nucleic acid with a mixture of a 3' exonuclease (+) DNA polymerase, particularly Taq polymerase, and a 3' exo (-) DNA polymerase, specifically Pfu, with dNTPs (200 μM) and salt buffer containing magnesium (see pages 22-23, 26) and triton X-100 (see table 17). Sorge teaches ratios of Taq to Pfu of 9:1, 7:3, 5:5, 3:7, and 1:9 in the composition and teaches the use of this composition in an amplification reaction comprising contacting the composition to a target nucleic acid to be amplified. Sorge teaches that all ratios of the two polymerases achieved amplification. The DNA polymerases were at a total concentration of 2.5 Units per 100 μL. Sorge teaches that the advantage of using the two polymerases is to reduce the number of mismatch errors that can occur with the thermostable polymerases.

Sorge does not specifically teach using this composition for nucleic acid sequencing. However Slatko teaches a method for nucleic acid thermal cycle dideoxy sequencing which uses a composition containing a thermostable polymerase such as Taq, VENT, Taq derivatives, DEEP VENT exo-, Pfu exo-, in a salt buffer containing MgCl, a non ionic surfactant, deoxynucleotides, and dideoxynucleotides (page 311). Slatko teaches that this sequencing method is a modification of dideoxynucleotide sequencing which incorporates the advantages of PCR amplification using thermostable polymerases to extend a primer by polymerization.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention as made to have applied the composition taught by Sorge to the thermal DNA sequencing method of Slatko in order to make the invention as a whole and to achieve the expected benefit of improving the fidelity of the sequencing reaction of Slatko to overcome the misincorporation problems associated with the error prone exo-thermostable polymerases as taught by Sorge.

Response to Arguments

14. The response traverses the rejection. The response asserts that because Sorge does not disclose, suggest or contemplate all of the claim limitations, that Sorge is deficient as a primary reference. This argument has been thoroughly reviewed but was found unpersuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Sorge anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention.

Further, the response asserts that Slatko does not disclose, suggest or contemplate modifying the method of Sorge and that the examiner's motivation has missed the point of obviousness. These arguments have been thoroughly reviewed but were found unpersuasive. Firstly, as noted in the MPEP 2143.01 (May 2004 edition), in *Ruiz v. A.B. Chance Co.,* 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004), the court rejected the notion that "an express written motivation to combine must appear in the prior art references…". It is additionally noted, as stated in the MPEP 2145, "One cannot show non obviousness by attacking references individually where the rejections are based on a combination of references. *In re Keller,* 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 (USPQ 375 (Fed. Cir. 1986).

The response cites *In re Mills* to assert that 'the mere fact that an advantage might be realized by combining references does not mean that a skilled artisan would be motivated to do so." The response asserts that rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, "the Examiner has simply asserted that the compositions of Sorge can be combined with the method of Slatko to overcome the misincorporation problems associated with error pone exothermostable polymerase. This argument has been thoroughly reviewed but was found unpersuasive. A review of the rejection made in the previous office action reveals that the examiner did point to a specific teaching, the teaching of Sorge of the advantage of using two polymerases to reduce the number of mismatch errors that can occur with thermostable polymerases (page 4, lines 4-22; pages 19-20, 27), in providing the motivation to combine the references in making the rejection. This was not "simply asserted" but represents general knowledge of those skilled in the art and expressly

taught by the prior art. Additionally, Slatko teaches that the sequencing method disclosed therein was a modification of dideoxynucleotide sequencing which incorporated the advantages of PCR amplification. Therefore, given this general knowledge which was specifically cited by the examiner in the previous office action: a) Slatko teaches a sequencing method using advantages of PCR amplification, and b) Sorge teaches improved PCR by using two polymerases: 3'exo(-) DNA polymerase and 3' exo (+) polymerase, the rejection asserted that it would have been prima facie obvious to use the improved composition taught by Sorge in the thermal sequencing method of Slatko (which the office action stated was taught by Slatko to incorporate advantages of PCR amplification) to make the invention as a whole, that is: to sequence nucleic acids with an exo(+) polymerase and an exo(-) polymerase for the obvious advantage as taught by Sorge to improve the fidelity of the sequencing reaction of Slatko by overcoming the misincorporation problems associated with error prone thermostable polymerases. The methodology of each reference is similar in the sense that Sorge teaches PCR: thermostable polymerase extends primer by polymerization and Slatko teaches nucleic acid sequencing using a thermostable polymerase to extend a primer by polymerization. It would therefore have been obvious to use the improved composition of Sorge, which as taught by Sorge to improve the fidelity of the PCR reaction, in the sequencing method which incorporated the advantages of PCR amplification in using a thermostable polymerase to extend a primer by polymerization of Slatko, to improve the fidelity of the sequencing reaction of Slatko. Therefore, given the rejection made in the previous office action and reiterated above, the response's assertion that "there is absolutely *nothing* in *Sorge or Slatko* that would have motivated one of ordinary skill in the art to have used a composition comprising a thermostable 3'exo+ and a thermostable 3' exo- DNA polymerase

in a method of sequencing a nucleic acid molecule" is not found persuasive. The response states that the examiner has pointed to no objective evidence or sound scientific reasoning for motivation or to support the rejection's conclusionary statements and that the examiner's assumption is baseless. The arguments have been thoroughly reviewed but were found unpersuasive. First, it is noted that the motivation to combine the cited references is that which was previously stated in the prior office action and repeated above and was taken from teachings of the cited reference. Particularly, the knowledge generally available to one of ordinary skill in the art of the advantage of using a 3' exo(+) polymerase and a 3'exo(-) polymerase to reduce the number of mismatch errors that can occur with thermostable polymerases, as stated in the cited references and further cited by the examiner in the previous office action, would have provided motivation to one of ordinary skill in art to improve the fidelity of the sequencing reaction of Slatko by using the composition taught by Sorge. Therefore, the examiner has not simply 'assumed' that such motivation exists in the "general knowledge" without providing any basis, as asserted by the response, but instead specifically pointed to it in the rejection. Therefore, the motivation to combine was taught in the cited references and as such was "knowledge" that was generally available to those of ordinary skill in the art, and was therefore not 'baseless' as also asserted by the response. It is acknowledged that because Sorge does not teach a method of sequencing with the recited composition, Sorge does not meet the requirements of the claims. However, given the motivation taught by Sorge for using a 3' exo(+) polymerase and a 3'exo(-) polymerase to reduce the number of mismatch errors that can occur with thermostable polymerases, the ordinary artisan would have been motivated to use the composition to decrease incorporation of mismatched bases and thereby improve the fidelity of the sequencing reaction of

Slatko. For these reasons and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

15. Claims 1-2, 5, 6, 8-9, 18, 19, 24-28, 30, 33, 48, 49, and 53-55 are rejected under 35 USC 103(a) as being unpatentable over Lundberg in view of Sobol, Isner, and Vizard.

Lundberg teaches a composition for nucleic acid amplification comprising either Taq (claims 8-9) or Pfu DNA polymerase at 25 U/mL (claims 18-19), a salt buffer containing magnesium (claim 26), dNTPs at a concentration of 200 μM (claim 28)) and triton X-100 (claims 27 and 53-55) (see page 4, cols 1-2). "About 20 units/mL" of polymerase is interpreted to encompass 25 U/mL (instant claims 9 and 19). Lundberg teaches that the reactions were used in PCR to amplify nucleic acids (claims 33 and 40).

Lundberg does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules. However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard specifically teaches that these compositions do not contain nucleic acids and are

generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared the PCR reaction mixtures of Lundberg by first preparing a master mix composition including all reagents other than primers and template. The ordinary artisan would have been motivated to have made such a modification for the expected advantage of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, and thus could be used in any amplification reaction.

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Lundberg in view of Sobol, Isner and Vizard is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. Further, the composition taught by Lundberg in view of Sobol, Isner, and Vizard must be stable upon storage for some length of time because it is stable under the cycling temperatures of the PCR reaction such that the polymerase retains activity and the

reagents are stable to allow amplification of a target nucleic acid. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Lundberg in view of Sobol, Isner, and Vizard is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

16. The response traverses the rejection. The response asserts that a reason, suggestion, or motivation required for properly combining the cited references is lacking from the references themselves. This argument has been thoroughly reviewed but was found unpersuasive. As noted in the MPEP 2143.01 (May 2004 edition), in *Ruiz v. A.B. Chance Co.,* 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004), the court rejected the notion that "an express written motivation to combine must appear in the prior art references…".

The response asserts that since Lundberg fails to meet the limitations in the claims, that Lundberg is fatally deficient as a primary reference, noting that "the examiner herself admits, Lundberg does not disclose a composition that 'does not contain nucleic acid molecules'". This argument has been thoroughly reviewed but was found unpersuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Lundberg anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention.

The response asserts that the Examiner's reliance on Sobol, Isner and Vizard to provide the motivation is misplaced in that it mistakenly focuses on the preparation of a "master mix" of reagents in all of these references and that the disclosure of these references is not relevant to the

claimed invention. The response asserts that the focus on the preparation of master mixes in general loses sight of the elements of the claimed invention. The response asserts that the claims are not drawn to the concept of making such a 'master mix' but instead to novel and unobvious 'compositions' and that what makes the present invention nonobvious are that the components are present at 'working concentrations', not whether they are mixed prior to use. The response asserts that "a mixture of compositions comprising these components at working concentrations simply is not disclosed or suggested in the cited references, and one of ordinary skill in the art would not be motivated to make and use the presently claimed compositions. These arguments have been thoroughly reviewed but were not found persuasive. It appears that applicant is arguing that because applicant's purpose for making the instantly claimed compositions is different from the motivation to make the compositions in the rejection set forth in the previous office action, that the instantly claimed invention is not obvious over the cited references. However, as noted in the MPEP 2144, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant". The instant claims are drawn to products, therefore, the cited references and the knowledge generally available to one of ordinary skill in the art must merely suggest and provide a motivation to prepare compositions meeting the requirement of the claims. The fact that the reasons for preparing the claimed compositions relied upon in the office action and/or the steps required to prepares said compositions, differ from the reasons that motivated applicant and/or the steps employed by applicant, does not alter the fact that the compositions themselves are obvious. It is acknowledged that because

Lundberg does not disclose *the order* in which the reagents are combined, Lundberg does not disclose a combination meeting the requirement of the claims. However, it is noted that, as stated in the previous office, both the knowledge generally available to one of ordinary skill in the art that master mixes are typically used when performing multiple PCR and sequencing reactions in order to improve efficiency, and given that Isner teaches that the use of master mixes "results in greater accuracy and reproducibility" and the teachings of Vizard that the use of master mixes eliminates many steps and is far more amenable to automation and further the teaching of the use of master mixes that contain all reagents necessary other than nucleic acids (teachings of Sobol and Vizard), one of ordinary skill in the art would have been motivated to use a master mix when setting up the reactions of Lundberg for the purpose of improving the accuracy, efficiency, and reproducibility in conducting PCR amplification. With regard to the argument that the claims comprise compositions with components at "working concentrations", such is not found persuasive. The term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. The recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as amplification, sequencing, or digestion of nucleic acids)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Further, the term working concentration is not commonly used in the art to limit "functions" only to amplification, sequencing, or digestion of nucleic acids. The preambles of the claims merely recite an intended use of the claimed composition, which does not limit the components or the amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable

interpretation, the term is interpreted to encompass for example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master mix such that any dilution of the master mix would result in the reagents being present and ready for use in a reaction, in relation to each other, without need for further addition of those reagents. In other words, the reagents are present at concentrations to function in a master solution, and are therefore 'at a concentration to perform a particular function'. The master mix could be one for use in "nucleic acid synthesis, nucleic acid amplification, or sequencing" as set forth in the preamble. As the recitation of 'working concentration' is not limited in the art to be used only to define the concentration of a reagent while it is performing in a sequencing or amplification reaction, and the examiner has used the definition in the specification in interpreting the recitation, the term "working concentration" does not distinguish the concentration of the claimed reagents from those taught in the cited references.

The response asserts that the logic employed by the examiner would render "compositions comprising any combination of more than one component" obvious "if the components were mixed prior to use". This argument has been thoroughly reviewed but was found unpersuasive. The motivation cited by the examiner is not a general motivation and would not be applicable to any combination of more than one component. The motivation cited in the rejection are specific to compositions of a particular type, that is those used in PCR or nucleic acid sequencing, for example. Lundberg teaches a method of PCR, and the use of master mixes including those components required in multiple reactions (enzyme, buffer, dNTPs, etc) and excluding those components required only for specific amplification (template, primers) was

extremely well known and widely practiced in laboratories that conduct PCR at the time the invention was made. The ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a master mix composition that could be successfully employed with a variety of different templates and primers and which could therefore be used in any amplification reaction. The rejection in no way asserted that the invention was obvious "solely because it is a combination of elements that were known in the art at the time the invention was made" as is asserted by the response. Instead, the rejection set for a specific motivation for preparing the compositions of the instant claims drawn from both the teachings in the art and the knowledge generally available to one of ordinary skill in the art and further cited such in the previous office action and reiterated above. Given the teachings of Sobol, Isner, and Vizard, the ordinary artisan would have been motivated to have prepared a master mix using the components taught by Lundberg, but excluding nucleic acids to improve the efficiency, accuracy, and reproducibility when practicing the methods of Lundberg.

The response asserts that the examiner is attempting to use Applicants' own specification, rather than the cited art, to find motivation to combine the cited references. As noted above, however, this is not the case. The examiner specifically used the teachings of the cited art and the motivation taught in the cited art as motivation for combining the references. In fact, as noted by the response at pages 31-32, the motivation to combine the references used by the office action is different than that used by applicants and taught in the specification. Thus, the response's assertion that the examiner has used 'improper hindsight analysis' is not persuasive. Further, it must be recognized that any judgment on obviousness is in a sense necessarily a

reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For these reasons and the reasons made of record in the previous office action, the rejection is maintained.

17. Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lundberg in view of Sobol, Isner, and Vizard as applied to claims 1-2, 5, 6, 8, 9, 18, 19, 24-28, 30, 33, 40, 48-49, and 53-55 above, and further in view of Hughes et al (hereinafter referred to as Hughes, WO 96/10640).

The teachings of Lundberg in view of Sobol, Isner, and Vizard are set forth above. Lundberg in view of Sobol, Isner, and Vizard do not teach using Tne DNA polymerase. However, Hughes teaches the use of Tne thermostable DNA polymerase, and mutants of such, in DNA amplification and sequencing reactions. Furthermore, Hughes teaches kits which comprise the Tne polymerase, dNTPs, and ddNTPs and no nucleic acid molecules. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the compositions of Lundberg in view of Sobol, Isner and Vizard to include compositions that contained Tne polymerase as Hughes teaches that such polymerase is useful in DNA amplification and sequencing reactions.

Response to Arguments

18. The response traverses the rejection. The response incorporates and reiterates previous arguments made with regard to Lundberg, Sobol, Isner, and Vizard. The response asserts that

these deficiencies are not cured by the teachings of Hughes because Hughes only discloses the use of Tne thermostable DNA polymerase in DNA amplification and sequencing reactions. These arguments have been thoroughly reviewed but were found unpersuasive for the reasons already made of record above. Additionally, as stated in the previous office action and reiterated above, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the compositions of Lundberg in view of Sobol, Isner, and Vizard, to include compositions that included Tne polymerase as Hughes teaches that such is useful in DNA amplification and sequencing reactions. The response asserts that Hughes does not disclose, suggest, or otherwise contemplate compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. This argument has been thoroughly reviewed but was found unpersuasive. Firstly, as noted in the MPEP 2143.01 (May 2004 edition), in *Ruiz v. A.B. Chance Co.,* 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004), the court rejected the notion that "an express written motivation to combine must appear in the prior art references…". It is additionally noted, as stated in the MPEP 2145, "One cannot show non obviousness by attacking references individually where the rejections are based on a combination of references. *In re Keller,* 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 (USPQ 375 (Fed. Cir. 1986). For these reasons and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

19. Claims 1-2, 5, 6, 8-11, 18, 19, 24-28, 30, 33, 40, 48, 49, and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes in view of Lundberg , Sobol , Isner, and Vizard.

Hughes teaches the use of Tne thermostable DNA polymerase, and mutants of such, in DNA amplification and sequencing reactions. Furthermore, Hughes teaches kits which comprise the Tne polymerase, dNTPs, and ddNTPs and no nucleic acid molecules.

Hughes does not teach a composition that contains a mixture of polymerase, dNTPs, and ddNTPs, and contains no nucleic molecules, however, However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to

have improved the PCR or sequencing kit Hughes by included a premixed composition that contains polymerase, dNTPs, and optionally ddNTPs for the obvious improvement of providing the user with a premixed solution that would require less steps (mixing the components of the kit of Hughes, together) in carrying out the method. Furthermore, the ordinary artisan would have been motivated to have made such a modification for the expected advantage of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Lundberg demonstrates concentrations of reagents for PCR, and Vizard demonstrates concentrations of reagents for sequencing

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Hughes in view of Sobol, Isner, Vizard and Lundberg is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Hughes in view of Sobol, Isner, Vizard, and Lundberg is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

20. The response traverses the rejection. The response incorporates and reiterates previous arguments made with regard to Lundberg, Sobol, Isner, Vizard and Hughes. These arguments have been thoroughly reviewed but were found unpersuasive for the reasons already made of

record above. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

21. Claims 2, 5, 6, 8, 18, 24-28, 30, 33, 45-47, 49, 51, and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scalice in view of Sobol, Isner, and Vizard.

Scalice teaches a composition containing Taq DNA polymerase (50 U/mL) (instant claims 8, 18), Tris buffer with MgCl (instant claim 26), Nonidet P-40 nonionic surfactant, Tween (instant claims 27, 53-57), dNTPs (200 μM) (instant claim 28), and an antibody (claims 44-47) which binds to Taq polymerase (see col. 15, lines 42-65). Scalice specifically teaches packaging reagents in a kit (col 3, lines 15-30; instant claim 30) and teaches PCR reactions (col. 3, lines 32-50; instant claim 34) for amplification of target DNA (examples 1 and 2; instant claim 40). Scalice further teaches using different thermostable polymerases such as Pfu (col. 7, lines 7-11; instant claim 6).

Scalice does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules. However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard

teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared the PCR reaction mixtures of Scalice by first preparing a master mix composition including all reagents other than primers and template. The ordinary artisan would have been motivated to have made such a modification for the expected advantage of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, and thus could be used in any amplification reaction.

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Scalice in view of Sobol, Isner and Vizard is the same as the instantly claimed composition, such are considered to have the same

properties and characteristics. Further, the composition taught by Scalice in view of Sobol, Isner, and Vizard must be stable upon storage for some length of time because it is stable under the cycling temperatures of the PCR reaction such that the polymerase retains activity and the reagents are stable to allow amplification of a target nucleic acid. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Scalice in view of Sobol, Isner, and Vizard is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

22. The response traverses the rejection. The response reiterates and incorporates arguments made previously with regard to Scalice. These arguments have been thoroughly reviewed but are found unpersuasive for the reasons already made of record above. The response asserts that because Scalice does not teach, suggest or otherwise contemplate compositions comprising a mixture of reagents at working concentrations that have no nucleic acids, that Scalice is deficient as a primary reference. This argument has been thoroughly reviewed but was found unpersuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Scalice anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention. The response further reiterates and incorporates the arguments made previously with regard to Sobol, Isner, and Vizard. These arguments have been thoroughly reviewed but were found unpersuasive for the reasons made of record above. For these reasons,

and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

23. Claims 1, 2, 5-9, 14-19, 22-26, 28, 33, 37-43, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes et al (hereinafter referred to as Barnes; PNAS, vol. 91, pp 2216-2220, 1994) in view of Sobol, Isner, and Vizard.

Barnes teaches a stable composition for nucleic acid amplification comprising a mutant form of Taq, Klentaql, which is exonuclease free and Pfu DNA polymerase, a salt buffer which contains magnesium and 250 μM dNTPs (page 2217, col. 1, para 2). Barnes also teaches compositions containing VENT and DEEP VENT DNA polymerases in combination with a Taq polymerase (page 2218, col. 2). Barnes teaches that this composition was used to amplify long nucleic acids (claims 33 and 40) larger than 8 kb (claims 37-39 and 41-43).

Barnes does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules. However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard

specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared the PCR reaction mixtures of Barnes by first preparing a master mix composition including all reagents other than primers and template. The ordinary artisan would have been motivated to have made such a modification for the expected advantage of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, and thus could be used in any amplification reaction.

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Barnes in view of Sobol, Isner and Vizard is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. Further, the composition taught by Barnes in view of Sobol, Isner, and Vizard must be stable upon storage for some length of time because it is stable under the

cycling temperatures of the PCR reaction such that the polymerase retains activity and the reagents are stable to allow amplification of a target nucleic acid. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Barnes in view of Sobol, Isner, and Vizard is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

24. The response traverses the rejection. The response asserts that Barnes discloses compositions that have nucleic acids and does not disclose, suggest or otherwise contemplate a composition comprising a mixture of reagents at working concentrations that have no nucleic acid molecules and is therefore deficient as a primary reference. These arguments have been thoroughly reviewed but are not found persuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Barnes anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention. Additionally, with regard to the argument that the claims comprise compositions with components at "working concentrations", such is not found persuasive to overcome the rejection. The term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. The recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as amplification, sequencing, or digestion of nucleic acids)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Further, the

term working concentration is not commonly used in the art to limit "functions" only to amplification, sequencing, or digestion of nucleic acids. The preambles of the claims merely recite an intended use of the claimed composition, which does not limit the components or the amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable interpretation, the term is interpreted to encompass for example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master mix such that any dilution of the master mix would result in the reagents being present and ready for use in a reaction, in relation to each other, without need for further addition of those reagents. In other words, the reagents are present at concentrations to function in a master solution, and are therefore 'at a concentration to perform a particular function'. The master mix could be one for use in "nucleic acid synthesis, nucleic acid amplification, or sequencing" as set forth in the preamble. As the recitation of 'working concentration' is not limited in the art to be used only to define the concentration of a reagent while it is performing in a sequencing or amplification reaction, and the examiner has used the definition in the specification in interpreting the recitation, the term "working concentration" does not distinguish the concentration of the claimed reagents from those taught in the cited references. The response reiterates and incorporates the arguments made with regard to Sobol, Isner and Vizard. These arguments have been thoroughly reviewed but were not found persuasive for the reasons made of record above. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

25. Claims 1, 2, 5, 12, 13, 24-26, 33, 40, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al (hereinafter referred to as Gelfand; US Patent 5,420,029) in view of Sobol, Isner, and Vizard.

Gelfand teaches a stable composition for nucleic acid amplification comprising 25 U/mL of Tma polymerase, a salt buffer containing magnesium and 200 μM dNTPs which was used to amplify template nucleic acid.

Gelfand does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules. However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the

invention was made to have prepared the PCR reaction mixtures of Gelfand by first preparing a master mix composition including all reagents other than primers and template. The ordinary artisan would have been motivated to have made such a modification for the expected advantage of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, and thus could be used in any amplification reaction.

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Gelfand in view of Sobol, Isner and Vizard is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. Further, the composition taught by Gelfand in view of Sobol, Isner, and Vizard must be stable upon storage for some length of time because it is stable under the cycling temperatures of the PCR reaction such that the polymerase retains activity and the reagents are stable to allow amplification of a target nucleic acid. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Gelfand in view of Sobol, Isner, and Vizard is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

26. The response traverses the rejection. The response asserts that Gelfand discloses compositions that have nucleic acids and does not disclose, suggest or otherwise contemplate a composition comprising a mixture of reagents at working concentrations that have no nucleic acid molecules and is therefore deficient as a primary reference. These arguments have been thoroughly reviewed but are not found persuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Gelfand anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention. Additionally, with regard to the argument that the claims comprise compositions with components at "working concentrations", such is not found persuasive to overcome the rejection. The term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. The recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as amplification, sequencing, or digestion of nucleic acids)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Further, the term working concentration is not commonly used in the art to limit "functions" only to amplification, sequencing, or digestion of nucleic acids. The preambles of the claims merely recite an intended use of the claimed composition, which does not limit the components or the amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable interpretation, the term is interpreted to encompass for

example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master mix such that any dilution of the master mix would result in the reagents being present and ready for use in a reaction, in relation to each other, without need for further addition of those reagents. In other words, the reagents are present at concentrations to function in a master solution, and are therefore 'at a concentration to perform a particular function'. The master mix could be one for use in "nucleic acid synthesis, nucleic acid amplification, or sequencing" as set forth in the preamble. As the recitation of 'working concentration' is not limited in the art to be used only to define the concentration of a reagent while it is performing in a sequencing or amplification reaction, and the examiner has used the definition in the specification in interpreting the recitation, the term "working concentration" does not distinguish the concentration of the claimed reagents from those taught in the cited references. The response reiterates and incorporates the arguments made with regard to Sobol, Isner and Vizard. These arguments have been thoroughly reviewed but were not found persuasive for the reasons made of record above. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

27. Claims 1, 2, 6, 20, 24-26, 28, 33, 40, and 48-49 rejected under 35 U.S.C. 103(a) as being unpatentable over Hinnisdaels et al (hereinafter referred to as Hinnisdaels, BIOTECHNIQUES, vol. 20, 1996, p 186, 188) in view of Sobol, Isner, and Vizard.

Hinnisdaels teaches a composition for amplification and a method for amplification containing Pwo Thermostable DNA polymerase, a salt buffer containing magnesium, 200 μM dNTP and about 100 μM polymerase (page 186, col. 3).

Hinnisdaels does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules. However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared the PCR reaction mixtures of Hinnisdaels by first preparing a master mix composition including all reagents other than primers and template. The ordinary artisan would have been motivated to have made such a modification for the expected advantage

of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, and thus could be used in any amplification reaction.

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Hinnisdaels in view of Sobol, Isner and Vizard is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. Further, the composition taught by Hinnisdaels in view of Sobol, Isner, and Vizard must be stable upon storage for some length of time because it is stable under the cycling temperatures of the PCR reaction such that the polymerase retains activity and the reagents are stable to allow amplification of a target nucleic acid. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Hinnisdaels in view of Sobol, Isner, and Vizard is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

28. The response traverses the rejection. The response asserts that Hinnisdaels discloses composition s that have nucleic acids and does not disclose, suggest or otherwise contemplate a composition comprising a mixture of reagents at working concentrations that have no nucleic

acid molecules and is therefore deficient as a primary reference. These arguments have been thoroughly reviewed but are not found persuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Hinnisdaels anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention. Additionally, with regard to the argument that the claims comprise compositions with components at "working concentrations", such is not found persuasive to overcome the rejection. The term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. The recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as amplification, sequencing, or digestion of nucleic acids)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Further, the term working concentration is not commonly used in the art to limit "functions" only to amplification, sequencing, or digestion of nucleic acids. The preambles of the claims merely recite an intended use of the claimed composition, which does not limit the components or the amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable interpretation, the term is interpreted to encompass for example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master mix such that any dilution of the master mix would result in the reagents being present and ready for use in a reaction, in relation to each other, without need for further addition of those reagents. In other

words, the reagents are present at concentrations to function in a master solution, and are therefore 'at a concentration to perform a particular function'. The master mix could be one for use in "nucleic acid synthesis, nucleic acid amplification, or sequencing" as set forth in the preamble. As the recitation of 'working concentration' is not limited in the art to be used only to define the concentration of a reagent while it is performing in a sequencing or amplification reaction, and the examiner has used the definition in the specification in interpreting the recitation, the term "working concentration" does not distinguish the concentration of the claimed reagents from those taught in the cited references. The response reiterates and incorporates the arguments made with regard to Sobol, Isner, and Vizard. These arguments have been thoroughly reviewed but were not found persuasive for the reasons made of record above. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

29. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hinnisdaels in view of Sobol, Isner, and Vizard as applied to claims 1-2, 6, 20, 24-26, 28, 33, 40, and 48-49 above, and further in view of Lundberg.

The teachings of Hinnisdaels in view of Sobol, Isner, and Vizard are set forth above. Hinnisdaels in view of Sobol, Isner, and Vizard do not teach a composition comprising a Pwo polymerase wherein in the concentration of the polymerase is "about 20 units/milliliter". However, Lundberg demonstrates PCR amplification with polymerases at 25 units/mL. Therefore, it would have bee prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Hinnisdaels in view of Sobol, Isner, and

Vizard to include compositions wherein the polymerase was 25 units/mL as taught by Lundberg for the expected advantage of using an effective amount of polymerase to achieve amplification, without wasting unnecessary extra polymerase. The ordinary artisan would have been motivated to determine the concentration of polymerase needed to carry out effective amplification for the purposes of not wasting enzyme. As stated in the MPEP (2144.05),

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")".

Further, as Lundberg teaches that amplification can be achieved with polymerases at 25 units/mL, the ordinary artisan would have had a reasonable expectation of success that the Pwo polymerase could function at such concentration in a method of amplification.

Response to Arguments

30. The response traverses the rejection. The response reiterates and incorporates the arguments made with regard to Hinnisdaels, Sobol, Isner, Vizard, and Lundberg. These arguments have been thoroughly reviewed but were not found persuasive for the reasons made of record above. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

31. Claims 1, 2, 5, 8, 24-26, 28, 33, 40, 48, and 49 are rejected under 35 U.S.C. 103(a) as unpatentable Heath et al (hereinafter referred to as Heath; Nucleic Acids Research, vol 21, pp 5782-5785; 1993) in view of Sobol, Isner, and Vizard.

Heath teaches a stable composition for nucleic acid amplification comprising a mixture of Taq polymerase (a thermostable DNA polymerase), a salt buffer of Tris, KCL and MgCl and deoxynucleotides (page 5782, col. 2, para 2). The concentration of Taq polymerase was 0.5 U/μL which is 50 units/mL (claim 8) and the concentration of dNTPs was 200 μM (claim 28). Heath teaches that this composition was used in PCR reactions with template nucleic acid in order to amplify the nucleic acid (claims 33 and 40).

Heath does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules. However, Sobol discloses the use of master mixes of reagents while preparing multiple samples for PCR (see col. 17, lines 19-44), wherein the master mix includes all PCR reagents, including polymerase, other than primers and template. It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. For example, Isner discloses the use of master mixes in the preparation of enzymatic reactions mixtures results in "greater accuracy and reproducibility (see col. 15, lines 37-39). Also, Vizard teaches making master mix compositions and kits comprising such compositions that contain all reagents necessary for nucleic acid sequencing, including polymerase, other than DNA template. Vizard specifically teaches that these compositions do not contain nucleic acids and are generated to simply add DNA to the solution, which eliminates many steps (ie, adding each component every time a reaction is carried out) and is far more amenable to automation (see page 6). Vizard

teaches packaging such composition in kit format (p. 10, 19), without the need for dilution steps for convenience to the user. In view of the teachings of Sobol, Isner, and Vizard, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared the PCR reaction mixtures of Heath by first preparing a master mix composition including all reagents other than primers and template. The ordinary artisan would have been motivated to have made such a modification for the expected advantage of improving the efficiency, accuracy, and reproducibility in conducting PCR amplification. The ordinary artisan would have been motivated to prepare such master mixes at "working concentrations" in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions. Further, the ordinary artisan would have been motivated to have prepared a master mix including all the reagents except for primers and template in order to have possessed a single master mix composition that could be successfully employed with a variety of different templates and primers, and thus could be used in any amplification reaction.

With regard to claims 48 and 49, the claimed recitations are drawn to properties of the claimed composition. Since the composition taught by Heath in view of Sobol, Isner and Vizard is the same as the instantly claimed composition, such are considered to have the same properties and characteristics. Further, the composition taught by Heath in view of Sobol, Isner, and Vizard must be stable upon storage for some length of time because it is stable under the cycling temperatures of the PCR reaction such that the polymerase retains activity and the reagents are stable to allow amplification of a target nucleic acid. With regard to claims 24 and 25, the claimed recitations are drawn to properties of the claimed composition. Since the composition

taught by Heath in view of Sobol, Isner, and Vizard is the same as the instantly claimed composition, such are considered to have the same properties.

Response to Arguments

32. The response traverses the rejection. The response asserts that Heath discloses compositions that have nucleic acids and does not disclose, suggest or otherwise contemplate a composition comprising a mixture of reagents at working concentrations that have no nucleic acid molecules and is therefore deficient as a primary reference. These arguments have been thoroughly reviewed but are not found persuasive. Under 35 USC 103, there is no requirement that a single reference "meet the limitations in the claims". The rejection in the previous office action did not assert that Heath anticipated the claimed invention, or alone rendered the claimed invention obvious. As set forth in the previous office action, it is the combination of the cited teachings in the prior art that suggest the claimed invention. Additionally, with regard to the argument that the claims comprise compositions with components at "working concentrations", such is not found persuasive to overcome the rejection. The term "working concentration" has been defined by the specification as the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function. The recitation of particular functions in the specification as set forth in parenthesis after the definition, "(such as amplification, sequencing, or digestion of nucleic acids)", are examples of "functions" and do not limit the term 'working concentration' to any specific or particular function. Further, the term working concentration is not commonly used in the art to limit "functions" only to amplification, sequencing, or digestion of nucleic acids. The preambles of the claims merely recite an intended use of the claimed composition, which does not limit the components or the

amounts of each component of the composition. Therefore, giving the term "working concentration" its broadest reasonable interpretation, the term is interpreted to encompass for example, reagents at concentrations used in a solution to perform any function. The function could be one where reagents are at concentrations relative to each other in a master mix such that any dilution of the master mix would result in the reagents being present and ready for use in a reaction, in relation to each other, without need for further addition of those reagents. In other words, the reagents are present at concentrations to function in a master solution, and are therefore 'at a concentration to perform a particular function'. The master mix could be one for use in "nucleic acid synthesis, nucleic acid amplification, or sequencing" as set forth in the preamble. As the recitation of 'working concentration' is not limited in the art to be used only to define the concentration of a reagent while it is performing in a sequencing or amplification reaction, and the examiner has used the definition in the specification in interpreting the recitation, the term "working concentration" does not distinguish the concentration of the claimed reagents from those taught in the cited references. The response reiterates and incorporates the arguments made with regard to Sobol, Isner and Vizard. These arguments have been thoroughly reviewed but were not found persuasive for the reasons made of record above. For these reasons, and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

Conclusion

33. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

34. No claims are allowable over the cited prior art.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

Note: The examiner's name has changed from Jehanne Souaya to Jehanne Sitton. All future correspondence to the examiner should reflect the change in name.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Jehanne Si Hon

Jehanne Sitton
Primary Examiner
Art Unit 1634
6/28/04